=> d his

(FILE 'HOME' ENTERED AT 10:32:14 ON 20 MAR 2003)

FILE 'REGISTRY' ENTERED AT 10:32:27 ON 20 MAR 2003
E "ENOXAPARIN"/CN 25
L1 2 S E3 OR E4

FILE 'CAPLUS' ENTERED AT 10:32:48 ON 20 MAR 2003
L2 21300 S L1
L3 60 L2 AND METALLOPROTEINASE?
L4 36 L3 AND (COLLAGENASE? OR AGGRECANASE? OR GELATINASE? OR MMP)

=> d l4 total ibib abs hitstr

L4 ANSWER 1 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:710798 CAPLUS
DOCUMENT NUMBER: 137:380428
TITLE: Involvement of HB-EGF and EGF receptor transactivation in TGF-β-mediated fibronectin expression in mesangial cells
AUTHOR(S): Uchiyama-Tanaka, Yoko; Matsubara, Hiroaki; Mori, Yasukiyo; Kosaki, Atsushi; Kishimoto, Noriko; Amano, Katsuya; Higashiyama, Shigeki; Iwasaka, Toshiji
CORPORATE SOURCE: Department of Medicine II, Kansai Medical University, Osaka, Japan
SOURCE: Kidney International (2002), 62(3), 799-808
CODEN: KDYIA5; ISSN: 0085-2538
PUBLISHER: Blackwell Publishing, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Gq-coupled receptors are known to transactivate epidermal growth factor receptor (EGFR) via the Ca2+ and PKC pathways to phosphorylate extracellular signal-regulated kinase (ERK). The authors studied the involvement of EGFR in transforming growth factor-β (TGF-β)-mediated fibronectin (FN) expression using glomerular mesangial cells. TGF-β up-regulated FN mRNA accumulation in a time- and dose-dependent manner, which was completely inhibited by phosphatidylcholine-phospholipase C (PC-PLC) inhibitor and PKC inhibitors (calphostin-C and staurosporin). The EGFR inhibitor AG1478 completely abolished TGF-β-mediated FN expression. ERK inactivation by PD98059, and p38MAPK inhibitor SB203580 also showed significant inhibitory effects. Addition of neutralizing anti-heparin-binding EGF-like growth factor (HB-EGF) antibody, pretreatment with heparin and the **metalloproteinase** (**MMP**) inhibitor batimastat blocked FN expression. In mesangial cells stably transfected with a chimera containing HB-EGF and alkaline phosphatase (ALP) genes, ALP activity in incubation medium was rapidly increased by TGF-β (2.1-fold at 0.5 min) and reached a 3.7-fold increase at two minutes, which was abolished by calphostin-C or batimastat. TGF-β phosphorylated EGFR, ERK and p38MAPK in a PKC- and **MMP**-dependent manner. Smad2 phosphorylation by TGF-β was not affected by AG1478, and HB-EGF did not activate Smad2. FN mRNA stability was not affected by TGF-β. Cycloheximide did not interfere with TGF-β-mediated FN expression. The present study demonstrated that HB-EGF processed and released via PC-PLC-PKC signaling is an intermediate mol. for TGF-β-mediated EGFR transactivation, and subsequent activation of ERK

and p38MAPK is involved in FN expression via transcriptional regulation without requiring new protein synthesis.

IT **9005-49-6**, Heparin, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(HB-EGF and EGF receptor transactivation involvement in TGF-β-mediated fibronectin expression in glomerular mesangial cells and mechanisms thereof)

RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:465826 CAPLUS
DOCUMENT NUMBER: 137:28331
TITLE: Use of low-molecular-weight heparin for treating osteoarthritis and other diseases
INVENTOR(S): Kern, Christopher; Hoerber, Christine; Bartnik, Eckart; Haus-Seuffert, Philipp
PATENT ASSIGNEE(S): Aventis Pharma Deutschland G.m.b.H., Germany
SOURCE: PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002047696	A1	20020620	WO 2001-EP14261	20011205
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002021935	A5	20020624	AU 2002-21935	20011205
US 2002128226	A1	20020912	US 2001-14472	20011214

PRIORITY APPLN. INFO.: DE 2000-10063006 A 20001216
WO 2001-EP14261 W 20011205

AB The invention discloses the use of low mol. heparin for producing medicaments for the prophylaxis and treatment of diseases in the course of which increased activity of at least one of the matrix **metalloproteinases** neutrophil **collagenase**, **aggrecanase**, hADAMTSI and **gelatinase** A are involved.

IT **9005-49-6**, Heparin, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(low-mol.-weight heparin for treating osteoarthritis and other diseases)

RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:445207 CAPLUS
DOCUMENT NUMBER: 138:1588
TITLE: ADAMTS1 cleaves aggrecan at multiple sites and is differentially inhibited by **metalloproteinase** inhibitors
AUTHOR(S): Rodriguez-Manzaneque, Juan Carlos; Westling, Jennifer; Thai, Shelley N.-M.; Luque, Alfonso; Knauper, Vera; Murphy, Gillian; Sandy, John D.; Iruela-Arispe, M. Luisa
CORPORATE SOURCE: Department of Molecular, Cell and Developmental Biology, Molecular Biology Institute, University of California at Los Angeles, Los Angeles, CA, 90095, USA
SOURCE: Biochemical and Biophysical Research Communications (2002), 293(1), 501-508
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English
AB ADAMTS1 is a secreted protein that belongs to the recently described ADAMTS (a disintegrin and metalloprotease with thrombospondin repeats) family of proteases. Evaluation of ADAMTS1 catalytic activity on a panel of extracellular matrix proteins showed a restrictive substrate specificity which includes some proteoglycans. Our results demonstrated that human ADAMTS1 cleaves aggrecan at a previously shown site by its mouse homolog, but we have also identified addnl. cleavage sites that ultimately confirm the classification of this protease as an "**aggrecanase**". Specificity of ADAMTS1 activity was further verified when a point mutation in the zinc-binding domain abolished its catalytic effects, and latency conferred by the prodomain was also demonstrated using a furin cleavage site mutant. Suppression of ADAMTS1 activity was accomplished with a specific monoclonal antibody and some metalloprotease inhibitors, including tissue inhibitor of **metalloproteinases** 2 and 3. Finally, we developed an activity assay using an artificial peptide substrate based on the interglobular domain cleavage site (E373-A) of rat aggrecan.
IT **9005-49-6**, Heparin, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ADAMTS1 cleaves aggrecan at multiple sites and is differentially inhibited by **metalloproteinase** inhibitors)
RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:855412 CAPLUS
DOCUMENT NUMBER: 136:196010
TITLE: Construction, Expression, and Characterization of a Baculovirally Expressed Catalytic Domain of Human Matrix **Metalloproteinase**-9

AUTHOR(S): Sadatmansoori, Sepideh; MacDougall, John; Khademi, Shahram; Cooke, Laurence S.; Guarino, Linda; Meyer, Edgar F.; Forough, Reza
CORPORATE SOURCE: Department of Biochemistry and Biophysics, Health Science Center, Texas A&M University, College Station, TX, 77843, USA
SOURCE: Protein Expression and Purification (2001), 23(3), 447-452
CODEN: PEXPEJ; ISSN: 1046-5928
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We report DNA construction, baculovirus expression, and partial characterization of a minienzyme form of the human matrix **metalloproteinase**-9 (**MMP**-9). The **MMP**-9 minienzyme gene construct consisting of the pre, pro, and catalytic domains of the **MMP**-9 was introduced into Sf9 insect cells using a baculovirus expression system. The expression of the recombinant **MMP**-9 minienzyme was evaporating to be approx. 0.8 mg/L of cell medium. The recombinant protein was purified using a single-step gelatin-Sepharose affinity column and yielded a highly stable and active minienzyme with gelatinolytic activity. Moreover, two interesting findings related to **MMP**-9 interactions with heparin and TIMP-1 resulted from our studies. First, the pro and catalytic domains of the human **MMP** -9 are not sufficient for heparin affinity. Second, in contrast to the prevailing consensus, TIMP-1 blockade of the enzymic activity of **MMP**-9 does not require prior binding to the C-terminus of its **MMP**-9 protein substrate. (c) 2001 Academic Press.

IT **9005-49-6**, Heparin, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(binding; construction, expression, and characterization of a baculovirally expressed catalytic domain of human matrix **metalloproteinase**-9)

RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:798040 CAPLUS
DOCUMENT NUMBER: 135:339222
TITLE: Inhibition of abnormal cell proliferation with camptothecin or a derivative, analog, metabolite, or prodrug thereof, and combinations including camptothecin
INVENTOR(S): Rubinfeld, Joseph
PATENT ASSIGNEE(S): Supergen, Inc., USA
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001080843	A2	20011101	WO 2001-US12848	20010419
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
US 6420378	B1	20020716	US 2000-553710	20000420
EP 1276479	A2	20030122	EP 2001-930607	20010419
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			

PRIORITY APPLN. INFO.: US 2000-553710 A1 20000420
US 1999-418862 A2 19991015
WO 2001-US12848 W 20010419

AB A method for treating diseases associated with abnormal cell proliferation comprises delivering to a patient in need of treatment a compound selected from 20(S)-comptothecin, an analog of 20(S)-comptothecin, a derivative of 20(S)-camptothecin, a prodrug of 20(S)-camptothecin, and pharmaceutically active metabolite of 20(S)-camptothecin, in combination with an effective amount of one or more agents selected form the group consisting of alkylating agent, antibiotic agent, antimetabolic agent, hormonal agent, plant-derived agent, anti-angiogenesis agent and biol. agent. The method can be used to treat benign tumors, malignant or metastatic tumors, leukemia and diseases associated with abnormal angiogenesis.

IT **9005-49-6**, Heparin, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(camptothecin or derivative, analog, metabolite, or prodrug thereof for inhibition of abnormal cell proliferation, and combinations including camptothecin)

RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L4 ANSWER 6 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:545502 CAPLUS
DOCUMENT NUMBER: 135:117219
TITLE: Hapten-coagulation agent-antineoplastic agent combinations for treating neoplasms
INVENTOR(S): Yu, Baofa
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001052868	A1	20010726	WO 2001-US1737	20010118

WO 2001052868 C2 20030116
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
US 2002044919 A1 20020418 US 2001-765060 20010117
PRIORITY APPLN. INFO.: US 2000-177024P P 20000119

AB Methods are provided for treating neoplasms, tumors and cancers, using one or more haptens and coagulation agents or treatments, alone or in combination with other anti-neoplastic agents or treatments. Also provided are combinations, and kits containing the combinations for effecting the therapy.

IT **9005-49-6**, Heparin, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hapten-coagulation agent-antineoplastic agent combinations for treating neoplasms)

RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:466608 CAPLUS
DOCUMENT NUMBER: 136:67862
TITLE: Expression and induction of **collagenases** (**MMP**-8 and -13) in plasma cells associated with bone-destructive lesions
AUTHOR(S): Wahlgren, Jaana; Maisi, Paivi; Sorsa, Timo; Sutinen, Meeri; Tervahartiala, Taina; Pirila, Emma; Teronen, Olli; Hietanen, Jarkko; Tjaderhane, Leo; Salo, Tuula
CORPORATE SOURCE: Faculty of Medicine and Biomedicum, University of Helsinki, Helsinki, FIN-00014, Finland
SOURCE: Journal of Pathology (2001), 194(2), 217-224
CODEN: JPTLAS; ISSN: 0022-3417
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Matrix **metalloproteinases** (**MMPs**) collectively degrade extracellular matrix and basement membrane proteins in chronic inflammation and bone-destructive lesions. This study examined the ability of Ig-producing plasma cells, typically present in sites of chronic inflammation, to express **collagenases** (**MMP**-8 and -13) in vivo and in vitro. Phorbol-12-myristate-13-acetate, interleukin-6, and tumor necrosis factor-α and heparin with the tumor promoter or cytokines potently enhanced (up to 9-fold) **MMP**-8 and -13 expression by the RPMI 8226 myeloma cell line, as evidenced by Western blotting and semi-quant. reverse transcriptase-polymerase chain reaction. Immunohistochem. anal. and in situ hybridization revealed that plasma

cells expressed **MMP**-8 and -13 focally in periapical granulomas, odontogenic cysts, and malignant plasmacytomas. **MMP**-8 and **MMP**-13 from plasma cells can participate in bone organic matrix destruction at sites of chronic inflammation and neoplastic growth. Since **MMP**-13 was more frequently expressed than **MMP**-8 in plasma cells of strongly recurring keratocysts and malignant plasmacytomas, it is concluded that plasma cell **MMP**-13 has a particularly important role in benign and malignant bone-destructive lesions.

IT **9005-49-6**, Heparin, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(heparin induced **MMP**-8 and **MMP**-13 expression in plasma cells associated with bone-destructive lesions)

RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:374233 CAPLUS
DOCUMENT NUMBER: 135:148983
TITLE: Heparin-Enhanced Zymographic Detection of Matrilysin and **Collagenases**
AUTHOR(S): Yu, Wei-hsuan; Woessner, J. Frederick, Jr.
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University of Miami School of Medicine, Miami, FL, 33101, USA
SOURCE: Analytical Biochemistry (2001), 293(1), 38-42
CODEN: ANBCA2; ISSN: 0003-2697
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Unlike the **gelatinases** (**MMP**-2 and -9), matrilysin (**MMP**-7) and **collagenases** (**MMP**-1 and -13) are difficult to detect at low levels in conventional casein or gelatin zymog. In this report, heparin was used to enhance the zymog. assays for **MMP**-7, -1, and -13. With the addition of heparin to the enzyme sample, **MMP**-7 can be detected at a level of 30 pg in transferrin zymog. and **MMP**-1 and -13 can be detected at a level of 0.2 ng in gelatin zymog. Carboxymethylated transferrin is used instead of casein as a substrate for assaying rat **MMP**-7. This substrate does not require a prerun step or substrate crosslinking to give uniform staining and clear band formation. It is necessary for heparin to run to the same region of the gel as the enzyme to produce its enhancing effect. For **MMP**-7 movement of heparin and enzyme is almost equal; for the **collagenases** it is necessary to add heparin to each well after the electrophoretic run is underway. Possible mechanisms of activity enhancement are discussed. (c) 2001 Academic Press.

IT **9005-49-6**, Heparin, biological studies
RL: ARU (Analytical role, unclassified); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study)
(heparin-enhanced zymog. detection of matrilysin and **collagenases**)

RN 9005-49-6 CAPLUS

CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:338762 CAPLUS
DOCUMENT NUMBER: 134:362292
TITLE: Methods of determining individual hypersensitivity to a pharmaceutical agent from gene expression profile
INVENTOR(S): Farr, Spencer
PATENT ASSIGNEE(S): Phase-1 Molecular Toxicology, USA
SOURCE: PCT Int. Appl., 222 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001032928	A2	20010510	WO 2000-US30474	20001103
WO 2001032928	A3	20020725		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-165398P P 19991105
US 2000-196571P P 20000411

AB The invention discloses methods, gene databases, gene arrays, protein arrays, and devices that may be used to determine the hypersensitivity of individuals to a given agent, such as drug or other chem., in order to prevent toxic side effects. In one embodiment, methods of identifying hypersensitivity in a subject by obtaining a gene expression profile of multiple genes associated with hypersensitivity of the subject suspected to be hypersensitive, and identifying in the gene expression profile of the subject a pattern of gene expression of the genes associated with hypersensitivity are disclosed. The gene expression profile of the subject may be compared with the gene expression profile of a normal individual and a hypersensitive individual. The gene expression profile of the subject that is obtained may comprise a profile of levels of mRNA or cDNA. The gene expression profile may be obtained by using an array of nucleic acid probes for the plurality of genes associated with hypersensitivity. The expression of the genes predetd. to be associated with hypersensitivity is directly related to prevention or repair of toxic damage at the tissue, organ or system level. Gene databases arrays and apparatus useful for identifying hypersensitivity in a subject are also disclosed.

IT **9005-49-6**, Enoxaparin, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(methods of determining individual hypersensitivity to a pharmaceutical agent
from gene expression profile)
RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L4 ANSWER 10 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:786221 CAPLUS
DOCUMENT NUMBER: 134:98498
TITLE: Effects of heparin on the growth, extracellular matrix and matrix **metalloproteinase** gene expression in rat hepatic stellate cells
AUTHOR(S): Li, Wencai; Zhang, Jinsheng; Huang, Guangeun; Zhu, Hongquang; Zhang, Xiarong; Zhang, Yuee
CORPORATE SOURCE: Dep. Pathology, Shanghai Medical Univ., Shanghai, 20003, Peop. Rep. China
SOURCE: Zhonghua Ganzangbing Zazhi (2000), 8(4), 200-202
CODEN: ZGZZFE; ISSN: 1007-3418
PUBLISHER: Chongqing Yike Daxue, Dier Linchuang Xueyuan
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB Objective: To study the effects of heparin on the growth, extracellular matrix and matrix **metalloproteinase** (**MMP**) gene expression in rat hepatic stellate cells (HSC). Methods: Activated HSC was treated by heparin or fetal calf serum without heparin. The cell growth was evaluated by actual cell count and BrdU-labeled immunocytochem. stain. The gene expressions of type I and IV procollagen, fibronectin, **MMP**-2 and membrane type matrix **metalloproteinase** (MT-**MMP**) were investigated by immunocytochem. stain and digoxigenin-labeled in situ hybridization technique, resp. In addition, the **gelatinase** activity of **MMP**-2 was examined by zymog. Results: Heparin could obviously reduce HSC growth, inhibit the synthesis of type I procollagen and fibronectin protein, and the gene expressions of type I procollagen, fibronectin and MT-**MMP**. The expressions of type IV procollagen, **MMP**-2 and **MMP**-2 activity were not affected by heparin. Conclusion: The results demonstrate that heparin can inhibit HSC proliferation, down-regulate interstitial collagen synthesis and inhibit MT-**MMP** gene expression.
IT **9005-49-6**, Heparin, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effects of heparin on growth, extracellular matrix, and matrix **metalloproteinase** gene expression in rat hepatic stellate cells)
RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L4 ANSWER 11 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:688045 CAPLUS
DOCUMENT NUMBER: 133:271734
TITLE: Inhibition of matrix **metalloproteinases** with polymers and pharmaceutical applications thereof
INVENTOR(S): Marchant, Nancy S.; Dickens, Elmer Douglas, Jr.; Kemp,

Shannon M.
PATENT ASSIGNEE(S): The B.F.Goodrich Company, USA
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000056283	A1	20000928	WO 2000-US7158	20000317

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-275314 A 19990324

AB Polymeric compns. and devices for reducing or inhibiting the undesired effects or activity of matrix **metalloproteinases** (**MMPs**) in the body. Suitable devices include stents, catheters, guidewires, implants, or similar devices having a polymeric coating capable of inhibiting or countering the activity or effects of matrix **metalloproteinases** throughout the body. The compns. may further include one or more pharmaceutical agent.

IT **9005-49-6**, Heparin, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(addnl. active agent; polymeric compns. and devices for inhibiting undesired effects of matrix **metalloproteinase**)
RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:587694 CAPLUS
DOCUMENT NUMBER: 134:36750
TITLE: Effect of heparin and related glycosaminoglycan on PDGF-induced lung fibroblast proliferation, chemotactic response and matrix **metalloproteinases** activity
AUTHOR(S): Sasaki, Masahiro; Kashima, Masayuki; Ito, Takefumi; Watanabe, Akiko; Sano, Masaaki; Kagaya, Manabu; Shioya, Takanobu; Miura, Mamoru
CORPORATE SOURCE: Second Department of Internal Medicine, Akita University School of Medicine, Akita, 010, Japan
SOURCE: Mediators of Inflammation (2000), 9(2), 85-91
CODEN: MNFLEF; ISSN: 0962-9351
PUBLISHER: Carfax Publishing
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Fibroblast migration, proliferation, extracellular matrix protein synthesis and degradation are the key events in various biol. and pathol. processes in pulmonary fibrosis. In addition, biopsy specimens from the lungs of patients with pulmonary fibrosis show increased nos. of mast cells which have metachromatic granules containing heparin, histamin and proteases. Little is known about how these products influence pulmonary fibrosis. In the present study, we investigated the effect of heparin and related glycosaminoglycans on PDGF-induced lung fibroblast proliferation and chemotactic response in vitro. In addition, we examined the effect of heparin on both the induction of matrix **metalloproteinases** (**MMPs**) and **MMPs** activity in lung fibroblasts in vitro. Heparin, de-N-sulfated heparin but not heparan sulfate inhibited PDGF-induced lung fibroblast proliferation. In contrast, only heparin inhibited PDGF-stimulated human lung fibroblast chemotaxis. Neg. charged poly-L-glutamic acid had no effect on either fibroblast proliferation or chemotaxis. Thus the neg. charge alone cannot account for the antiproliferative and antichemotactic effects of heparin. Furthermore, heparin and heparan sulfate also had no inhibitory effect on induction of **MMPs**, including **MMP**-1 (interstitial **collagenase**), **MMP**-2 (**gelatinase** A) and **MMP**-9 (**gelatinase** B). Only heparin inhibited both **MMP**-1 and **MMP**-2/**MMP**-9 activity. Addnl., tissue inhibitor of **metalloproteinase** type 1 (TIMP-1) and type 2 (TIMP-2) inhibited PDGF-stimulated human lung fibroblast chemotaxis. The ability of heparin to inhibit fibroblast chemotaxis may account for the inhibitory effect of heparin on **MMP** activity. The above results suggested that heparin and related glycosaminoglycans differentially regulate PDGF-induced lung fibroblast proliferation, chemotaxis and **MMPs** activity and further that these effects may have a key role in extracellular matrix remodeling in inflammatory lung disease.

IT **9005-49-6**, Heparin, biological studies **9005-49-6D**, Heparin, de-N-sulfated, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(heparin and glycosaminoglycans effect on lung fibroblast proliferation, chemotaxis, and matrix **metalloproteinases** activity)

RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:323468 CAPLUS
DOCUMENT NUMBER: 133:116359
TITLE: Interaction with Heparin and Matrix **Metalloproteinase** 2 Cleavage Expose a Cryptic Anti-adhesive Site of Fibronectin
AUTHOR(S): Watanabe, Kazuo; Takahashi, Hiroshi; Habu, Yoshiko; Kamiya-Kubushiro, Naoko; Kamiya, Sadahiro; Nakamura,

Hiroshi; Yajima, Hirofumi; Ishii, Tadahiro; Katayama, Takashi; Miyazaki, Kaoru; Fukai, Fumio
CORPORATE SOURCE: Nippi Research Institute of Biomatrix, Tokyo, 120-8601, Japan
SOURCE: Biochemistry (2000), 39(24), 7138-7144
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We recently found that fibronectin (FN) had a functional site [YTIYVIAL sequence in the heparin-binding domain 2 (Hep 2)] that was capable of suppressing the integrin-mediated cell adhesion to extracellular matrix. However, our results also indicated that this anti-adhesive site seemed to be usually buried within the Hep 2 domain structure because of its hydrophobic nature, raising a question as to the physiol. significance of the cryptic anti-adhesive activity of FN. The present study demonstrates that the cryptic anti-adhesive activity can be exposed through the physiol. processes. A 30-kDa chymotryptic FN fragment derived from Hep 2 domain (Hep 2 fragment), which had no effect on adhesion of MSV-transformed nonproducer 3T3 cell line (KN78) to FN, expressed the anti-adhesive activity after treatment with 6 M urea. Light scattering and CD measurements showed that the urea treatment induced the conformational change of the Hep 2 fragment from a more compact form to an unfolded one. Incubation of the Hep 2 fragment with heparin also induced similar conformational changes and expression of anti-adhesive activity. Addnl., both the urea and heparin treatments made the Hep 2 fragment and intact FN much more accessible to the polyclonal antibody (αIII14A), with a recognition site near the anti-adhesive site of FN. Specific cleavage of either the Hep 2 fragment or intact FN by matrix **metalloproteinase** 2 (**MMP**-2) released a 10-kDa fragment with the anti-adhesive activity, which was shown to have the exposed anti-adhesive site on the amino-terminal region. Thus, the cryptic anti-adhesive activity of FN can be expressed upon conformational change and proteolytic cleavage of Hep 2 domain.
IT **9005-49-6**, Heparin, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(anti-adhesive site of fibronectin can be exposed by interaction with heparin)
RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:160236 CAPLUS
DOCUMENT NUMBER: 132:291982
TITLE: Epidermal growth factor-like ligands differentially up-regulate matrix **metalloproteinase** 9 in head and neck squamous carcinoma cells
AUTHOR(S): O-Charoenrat, Pornchai; Modjtahedi, Helmout; Rhys-Evans, Peter; Court, William J.; Box, Gary M.; Eccles, Suzanne A.
CORPORATE SOURCE: Tumor Biology and Metastasis Group, Section of Cancer

Therapeutics, The Institute of Cancer Research, Surrey, SM2 5NG, UK
SOURCE: Cancer Research (2000), 60(4), 1121-1128
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: AACR Subscription Office
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Head and neck squamous cell carcinomas (HNSCCs) are characterized by a marked propensity for local invasion and dissemination to cervical lymph nodes, with distant metastases developing in 30-40% of cases. Overexpression of the epidermal growth factor receptor (EGFR/c-erbB-1) and/or its ligands and high levels of certain matrix **metalloproteinases** (**MMPs**) have been associated with poor prognosis. The aim of this study was to examine the effects of EGFR ligands on **gelatinase** expression and invasion in HNSCC cell lines. We tested epidermal growth factor (EGF), transforming growth factor α, betacellulin, heparin-binding EGF, and amphiregulin and measured expression of **gelatinases** **MMP**-9 and **MMP**-2 in an established squamous carcinoma cell line (Detroit-562) and in two cell lines newly derived from patients with head and neck cancers (SIHN-005A and SIHN-006). Incubation of the cell lines with EGF-like ligands up-regulated **MMP**-9 (but not **MMP**-2) expression as measured by semiquant. reverse transcription-PCR in a dose-dependent manner, with the effects being most marked in cells with high EGFR levels and undetectable in cells with low levels. Maximum stimulation was obtained in a concentration range of 10-100 nM. In addition, we confirmed by zymog. that gelatinolytic activity consistent with **MMP**-9 (Mr 92,000) was up-regulated in parallel with increases in gene expression. Betacellulin (which binds both to EGFR and c-erbB-4 receptors) consistently increased **MMP**-9 expression and activation to a significantly greater degree than the other four ligands when tested at equimolar concns. In parallel with **MMP**-9 up-regulation, all EGF-like ligands increased tumor cell invasion through Matrigel in in vitro Transwell assays. These activities were independent of ligand effects on cell proliferation. Antagonist (ICR62) or agonist (ICR9) anti-EGFR monoclonal antibodies, resp., inhibited or potentiated **MMP**-9 activity and tumor cell invasion induced by all ligands. Furthermore, a monoclonal antibody that neutralizes **MMP**-9 activity (Ab1) also inhibited ligand-induced invasion of HNSCC. We confirmed that tumor cell lines used in these studies (and a larger series not reported here) generally expressed multiple c-erbB receptors and ligands. These results indicate that autocrine or paracrine signaling through EGFR potentiates the invasive potential of HNSCC via the selective up-regulation and activation of **MMP**-9. Furthermore, ligands such as betacellulin (which is commonly expressed in HNSCC), which can bind to and activate other c-erbB receptors, may be especially potent in this regard.

IT **9005-49-6**, Heparin, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(heparin-binding EGF; epidermal growth factor-like ligands differentially up-regulate matrix **metalloproteinase** 9 in human head and neck squamous carcinoma cells)
RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:129351 CAPLUS
DOCUMENT NUMBER: 132:275858
TITLE: Heparan sulfate proteoglycans as extracellular docking molecules for matrilysin (matrix **metalloproteinase** 7)
AUTHOR(S): Yu, Wei-Hsuan; Woessner, J. Frederick, Jr.
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University of Miami School of Medicine, Miami, FL, 33101, USA
SOURCE: Journal of Biological Chemistry (2000), 275(6), 4183-4191
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Many matrix **metalloproteinases** (**MMPs**) are tightly bound to tissues; matrilysin (**MMP**-7), although the smallest of the **MMPs**, is one of the most tightly bound. The most likely docking mols. for **MMP**-7 are heparan sulfate proteoglycans on or around epithelial cells and in the underlying basement membrane. This is established by extraction expts. and confocal microscopy. The enzyme is extracted from homogenates of postpartum rat uterus by heparin/heparan sulfate and by heparinase III treatment. The enzyme is colocalized with heparan sulfate in the apical region of uterine glandular epithelial cells and can be released by heparinase digestion. Heparan sulfate and **MMP**-7 are expressed at similar stages of the rat estrous cycle. The strength of heparin binding by recombinant rat proMMP-7 was examined by affinity chromatog., affinity coelectrophoresis, and homogeneous enzyme-based binding assay; the KD is 5-10 nM. Zymog. measurement of **MMP**-7 activity is greatly enhanced by heparin. Two putative heparin-binding peptides have been identified near the C- and N-terminal regions of proMMP-7; however, mol. modeling suggests a more extensive binding track or cradle crossing multiple peptide strands. Evidence is also found for the binding of **MMP**-2, -9, and -13. Binding of **MMP**-7 and other **MMPs** to heparan sulfate in the extracellular space could prevent loss of secreted enzyme, provide a reservoir of latent enzyme, and facilitate cellular sensing and regulation of enzyme levels. Binding to the cell surface could position the enzyme for directed proteolytic attack, for activation of or by other **MMPs** and for regulation of other cell surface proteins. Dislodging **MMPs** by treatment with compds. such as heparin might be beneficial in attenuating excessive tissue breakdown such as occurs in cancer metastasis, arthritis, and angiogenesis.

IT **9005-49-6**, Heparin, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(heparin enhances activity of matrilysin)
RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:727821 CAPLUS
DOCUMENT NUMBER: 132:246062
TITLE: Effect of heparin on the production of matrix **metalloproteinases** and tissue inhibitors of **metalloproteinases** by human dermal fibroblasts
AUTHOR(S): Gogly, B.; Dridi, M.; Hornebeck, W.; Bonnefoix, M.; Godeau, G.; Pellat, B.
CORPORATE SOURCE: Laboratory of Physiopathology of Non-Mineralized Tissues, University Rene Descartes Paris V, U.F.R. Odontology, Montrouge, 92120, Fr.
SOURCE: Cell Biology International (1999), 23(3), 203-209
CODEN: CBIIEV; ISSN: 1065-6995
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The influence of heparin and a heparin fragment devoid of anticoagulant activity on the production of matrix **metalloproteinases** and tissue inhibitors of **metalloproteinases** by human dermal fibroblasts was studied. Doses (0.1-400 μg/mL) responses were performed and data obtained were similar whatever heparin or fragment was used. The basal expression of **collagenase** by fibroblasts decreased quasi-linearly with increasing doses of heparins from 1 to 400 μg/mL. TIMP-1 levels were not affected by supplementing serum free culture medium with heparins. On the contrary, at low concentration, i.e. 1-10 μg/mL, heparins stimulated the secretion of both 72-kDa **gelatinase** (1.4-1.6-fold) and particularly TIMP-2 (>4-fold). At high doses, **MMP**-2 and TIMP-2 production by fibroblasts returned to basal levels. These results suggested that the local concentration of heparin released by mast cells could be instrumental in modulating fibroblast growth and proteolytic phenotype. (c) 1999 Academic Press.
IT **9005-49-6**, Heparin, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(heparin effect on the production of **MMPs** and tissue inhibitors of **metalloproteinases** by human dermal fibroblasts)
RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 17 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:421561 CAPLUS
DOCUMENT NUMBER: 131:63228
TITLE: Use of fucan for regulating the reconstruction of connective tissues
INVENTOR(S): Senni, Karim; Pellat, Bernard; Gogly, Bruno; Blondin, Catherine; Letourneur, Didier; Jozefonvicz, Jacqueline; Sinquin, Corinne; Colliec-Jouault, Sylvia; Durand, Patrick
PATENT ASSIGNEE(S): Institut Francais de Recherche pour l'Exploitation de la Mer (IFREMER), Fr.; Centre National de la Recherche

Scientifique - CNRS; Universite Rene Descartes - Paris V
SOURCE: PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9932099	A2	19990701	WO 1998-FR2758	19981217
W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2772618	A1	19990625	FR 1997-16080	19971218
FR 2772618	B1	20000218		
AU 9917649	A1	19990712	AU 1999-17649	19981217
EP 1039916	A2	20001004	EP 1998-962487	19981217
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
BR 9813778	A	20001024	BR 1998-13778	19981217
JP 2001526309	T2	20011218	JP 2000-525090	19981217

PRIORITY APPLN. INFO.: FR 1997-16080 A 19971218
WO 1998-FR2758 W 19981217

AB The use of fucans for obtaining medicines for modulating fibroblastic metalloprotease and inhibiting leukocytic elastase is disclosed. Said medicines help activate collagen synthesis, inhibit proliferation of gingival fibroblasts, and activate proliferation of dermal fibroblasts. They are useful in particular for treating periodontal pathologies and dermal lesions. Fucan at a concentration of 10 μg mL inhibited the proliferation of gingival fibroblast and increased the proliferation of dermal fibroblasts over a 4 day period.

IT **9005-49-6**, Heparin, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(use of fucan for regulating reconstruction of connective tissues)
RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L4 ANSWER 18 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:336109 CAPLUS
DOCUMENT NUMBER: 131:128451
TITLE: Acidic fibroblast growth factor induces an antifibrogenic phenotype in human lung fibroblasts
AUTHOR(S): Becerril, Carina; Pardo, Annie; Montano, Martha; Ramos, Carlos; Ramirez, Remedios; Selman, Moises
CORPORATE SOURCE: Instituto Nacional de Enfermedades Respiratorias, Universidad Nacional Autonoma de Mexico, Mexico, Mex.
SOURCE: American Journal of Respiratory Cell and Molecular

Biology (1999), 20(5), 1020-1027
CODEN: AJRBEL; ISSN: 1044-1549
PUBLISHER: American Lung Association
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Acidic fibroblast growth factor (FGF-1), a prototype member of the heparin-binding growth factor family, influences proliferation, differentiation, and protein synthesis in different cell types. However, its possible role on lung extracellular matrix (ECM) metabolism has not been evaluated. Here, the authors examined the effects of FGF-1 and FGF-1 plus heparin on type I collagen, collagen-binding stress protein HSP47, interstitial **collagenase** (matrix **metalloproteinase** [**MMP**]-1), **gelatinase** A, and tissue inhibitor of **metalloproteinase** (TIMP)-1 and TIMP-2 expression by normal human lung fibroblasts. Heparin was used because it enhances the biol. activities of FGF-1. Fibroblasts were exposed either to 20 ng/mL FGF-1 plus 100 μg/mL heparin for 48 h or to FGF-1 or heparin alone. MRNA expression was analyzed by Northern blot. Collagen synthesis was evaluated by digestion of [3H]collagen with bacterial **collagenase**, **MMP**-1 by Western blot, and gelatinolytic activities by zymog. The results show that FGF-1 induced **collagenase** mRNA expression, which was strongly enhanced when FGF-1 was used with heparin. Likewise, both FGF-1 and FGF-1 plus heparin reduced by 70-80% the expression of type I collagen transcript, in part via effect on pro-α1(I) collagen mRNA stability. A downregulation of HSP47 gene expression was also observed Synthesis of collagen and **collagenase** proteins paralleled gene expression results. FGF-1 activities were abolished with genistein, a tyrosine kinase inhibitor. Neither FGF-1 nor FGF-1 plus heparin affected the expression of TIMP-1, TIMP-2, and **gelatinase** A. Thus, FGF-1, mostly in the presence of heparin, upregulates **collagenase** and downregulates type I collagen expression that might have a protective role in avoiding collagen accumulation during lung ECM remodeling.

IT **9005-49-6**, Heparin, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(acidic fibroblast growth factor in presence of heparin induces antifibrogenic phenotype in human lung fibroblasts via upregulation of **collagenase** and downregulation of type I collagen expression)

RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 19 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:277459 CAPLUS
DOCUMENT NUMBER: 130:324355
TITLE: Containers, process, and kits for determination of tumor antigen-specific cellular immune responses
INVENTOR(S): Kobayashi, Koji; Setoguchi, Yuji
PATENT ASSIGNEE(S): Sekisui Chemical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 9 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 11118805	A2	19990430	JP 1997-276166	19971008

PRIORITY APPLN. INFO.: JP 1997-276166 19971008

AB Title containers are endotoxin-free vacuum containers in which anticoagulants and tumor antigens are placed. Blood samples are sucked into the containers for determination of enzymes or cytokines produced by the reactions between tumor antigens and blood cells. Title kits comprise the vacuum containers and reagents for determination of the enzymes or cytokines. IL-2 and **MMP**-9 produced by the reaction between carcinoembryonic antigen and blood cells of colorectal carcinoma patients were detd.by ELISA using an endotoxin-free poly(ethylene terephthalate) container and anticoagulant heparin Na.

IT **9041-08-1**, Sodium heparin
RL: ARU (Analytical role, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(anticoagulant; endotoxin-free containers and kits for determination of tumor
antigen-induced production of enzymes or cytokines in blood cells)

RN 9041-08-1 CAPLUS

CN Heparin, sodium salt (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L4 ANSWER 20 OF 36 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:69008 CAPLUS

DOCUMENT NUMBER: 130:291293

TITLE: Pentosan polysulfate decreases proliferation and net extracellular matrix production in mouse mesangial cells

AUTHOR(S): Elliot, Sharon J.; Striker, Liliane J.; Stetler-Stevenson, William G.; Jacot, Terry A.; Striker, Gary E.

CORPORATE SOURCE: Renal Cell Biology Section, Metabolic Disease Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, USA

SOURCE: Journal of the American Society of Nephrology (1999), 10(1), 62-68
CODEN: JASNEU; ISSN: 1046-6673

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Glomerulosclerosis is characterized by extracellular matrix accumulation and is often associated with mesangial cell proliferation. Heparin-like mols. have been shown to decrease glomerulosclerosis in vivo, although their cellular site and mechanism of action is still unclear. In this study, a line of glomerular mesangial cells derived from normal mice was used to determine whether pentosan polysulfate (PPS) inhibited proliferation and altered extracellular matrix turnover. Cells treated with PPS showed a decrease in cell number beginning 24 h after treatment, which was maintained for 5 d. For matrix accumulation and degradation studies, cells were treated for 5 d and collagen types I and IV protein were measured by ELISA as well as matrix **metalloproteinases** (**MMP**) measured by zymog. Collagen types I and type IV were significantly

decreased in the media (P < 0.0001) and cell layer (P < 0.005) after treatment with PPS but not after treatment with heparin. By zymog., **MMP**-2 was significantly increased after treatment with PPS (P < 0.001) and heparin (P < 0.05). PPS and heparin also decreased **MMP** -9 (P < 0.001) after treatment. Reverse zymog. showed the presence of tissue inhibitors of **metalloproteinases** (TIMP)-1 and -2 in control mesangial cells. Treatment with PPS and heparin increased TIMP-1. In addition, TIMP-3 was found in the medium of treated but not control cells. In conclusion, PPS alters extracellular matrix turnover through the induction of **MMP**-2 and alterations in the TIMP profile and may be useful in decreasing progressive glomerulosclerosis.

IT **9005-49-6**, Heparin, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pentosan polysulfate decreases proliferation and net extracellular matrix production in mouse mesangial cells)

RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 21 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:760794 CAPLUS
DOCUMENT NUMBER: 130:134148
TITLE: Influence of heparin(s) on the interleukin-1-β-induced expression of **collagenase**, stromelysin-1, and tissue inhibitor of **metalloproteinase**-1 in human gingival fibroblasts
AUTHOR(S): Gogly, Bruno; Hornebeck, William; Groult, Nicole; Godeau, Gaston; Pellat, Bernard
CORPORATE SOURCE: Laboratory of Biology and Physiopathology, U.F.R. Odontology, University Rene Descartes, Montrouge, 92120, Fr.
SOURCE: Biochemical Pharmacology (1998), 56(11), 1447-1454
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Here, the authors describe the influence of heparin(s) on the interleukin-1-β (IL-1 β)-induced expression of **collagenase** (matrix **metalloproteinase**-1, **MMP** -1), stromelysin-1 (matrix **metalloproteinase**-3, **MMP**-3) and tissue inhibitor of matrix **metalloproteinase**-1 (TIMP-1) in human gingival fibroblasts (HGF). Amts. of secreted enzymes and inhibitors as well as their mRNA steady-state levels increased significantly following supplementation of HGF culture medium with 2 ng/mL of IL-1 β. Addition of heparin to cell culture medium 1 h following IL-1 β decreased **MMP** and TIMP-1 expression in a dose-dependent manner. The inhibitory effect of heparin was significant at a concentration as low as 1 μg/mL. These findings could be reproduced with a low Mr heparin fragment devoid of anticoagulant activity. Heparin and fragments might therefore reduce the excessive proteolytic capacity of the gingival fibroblast during inflammation and could be useful as pharmacol.

agent(s) in gingivitis and periodontitis.
IT **9005-49-6**, Heparin, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(heparin(s) effect on the IL-1β-induced expression of **collagenase**, stromelysin-1, and tissue inhibitor of **MMP** -1 in human gingival fibroblasts)
RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 22 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:400791 CAPLUS
DOCUMENT NUMBER: 129:160116
TITLE: **Collagenase**-3 (matrix **metalloproteinase**- 13) expression is induced in oral mucosal epithelium during chronic inflammation
AUTHOR(S): Uitto, Veli-Jukka; Airola, Kristiina; Vaalamo, Maarit; Johansson, Nina; Putnins, Edward E.; Firth, James D.; Salonen, Jukka; Lopez-Otin, Carlos; Saarialho-Kere, Ulpu; Kahari, Veli-Matti
CORPORATE SOURCE: Department of Oral Biological and Medical Sciences, University of British Columbia, Vancouver, BC, V6T 1Z3, Can.
SOURCE: American Journal of Pathology (1998), 152(6), 1489-1499
CODEN: AJPAA4; ISSN: 0002-9440
PUBLISHER: American Society for Investigative Pathology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Increased proliferation of mucosal epithelium during inflammation is associated with degradation of subepithelial connective tissue matrix and local invasion of the epithelial cells. Here we have studied, whether **collagenase**-3 (**MMP**-13), a collagenolytic matrix **metalloproteinase** with an exceptionally wide substrate specificity, is expressed in the epithelium of chronically inflamed mucosa. Examination of human gingival tissue sections from subjects with chronic adult periodontitis with in situ hybridization revealed marked expression of **MMP**-13 in basal cells of some epithelial rete ridges expanding into connective tissue. Immunohistochem. staining demonstrated that these cells also expressed strongly laminin-5, suggesting that they are actively migrating cells. A strong signal for **MMP**-13 mRNA was occasionally also noted in the suprabasal epithelial cells facing the gingival pocket, whereas no **collagenase**-1 (**MMP**-1) mRNA was detected in any areas of the epithelium. **MMP**-13 expression was also detected in fibroblast-like cells associated with collagen fibers of the inflamed subepithelial connective tissue. In organ culture of human oral mucosa, **MMP**-13 mRNA expression was observed in epithelial cells growing into connective tissue of the specimens. Regulation of **MMP**-13 expression was examined in cultured normal nonkeratinizing epithelial cells isolated from porcine periodontal ligament. In these cells, **MMP** -13 expression at the mRNA and protein level was potently enhanced (up to

sixfold) by tumor necrosis factor-α, transforming growth factor-β1, and transforming growth factor-α and by keratinocyte growth factor in the presence of heparin. In addition, plating periodontal ligament epithelial cells on type I collagen stimulated **MMP**-13 expression (sevenfold) as compared with cells grown on tissue culture plastic. The results of this study show, that expression of **MMP**-13 is specifically induced in undifferentiated epithelial cells during chronic inflammation due to exposure to cytokines and collagen. Thus, it is likely that **MMP**-13 expression is instrumental in the subepithelial collagenolysis and local invasion of the activated mucosal epithelium into the connective tissue.

IT **9005-49-6**, Heparin, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(matrix **metalloproteinase**-13 expression is induced in oral mucosal epithelium during chronic inflammation)

RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 23 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:237651 CAPLUS
DOCUMENT NUMBER: 126:258951
TITLE: Effect of glucose and heparin on mesangial α1 (IV) COLL and **MMP**-2/TIMP-2 mRNA expression
AUTHOR(S): Caenazzo, C.; Garbisa, S.; Onisto, M.; Zampieri, M.; Baggio, B.; Gambaro, G.
CORPORATE SOURCE: Institute of Histology and Embriology, Medical School, Padua, 35121, Italy
SOURCE: Nephrology, Dialysis, Transplantation (1997), 12(3), 443-448
CODEN: NDTREA; ISSN: 0931-0509
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mesangial cells are responsible for the synthesis of mesangial matrix as well as its degradation, which is mediated by a number of proteolytic activities, including **metalloproteinases** (**MMPs**). Imbalanced matrix protein metabolism may be responsible for mesangial expansion and glomerulosclerosis in diabetic nephropathy. Heparin prevents this complication. In human and murine mesangial cell cultures, RT-PCR was able to detect mRNA expression for a number of mols. involved in the mesangial extracellular matrix turnover: type IV collagen [α1 (IV)COLL], **MMP**-1, **MMP**-2, **MMP**-3, **MMP**-9 and **MMP**-10, and the tissue inhibitors TIMP-1 and TIMP-2. The expression of mRNA for α1 (IV)COLL and **MMP**-2/TIMP-2 balance was studied in human cells in the presence of high glucose and heparin. MRNAs for all the studied mols. were expressed at different levels. Interestingly, a shift in the balance of α1 (IV)COLL, **MMP**-2 and TIMP-2 was observed in high glucose, which was partially reversed by heparin supplementation. The new equilibrium was mostly due to the down-regulation of type IV collagen expression, rather than further reduction

of potential proteolysis. Our data, while extending the list of potential mediators of mesangial matrix catabolism, highlight a mol. mechanism by which the pathogenesis of diabetic nephropathy may be sustained, and at the same time suggest that heparin may have the potential to correct this abnormality.

IT **9005-49-6**, Heparin, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of glucose and heparin on mesangial α1 (IV) COLL and **MMP**-2/TIMP-2 mRNA expression)

RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L4 ANSWER 24 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:196235 CAPLUS
DOCUMENT NUMBER: 126:289936
TITLE: The hemopexin-like domain (C domain) of human **gelatinase** A (matrix **metalloproteinase** -2) requires Ca2+ for fibronectin and heparin binding. Binding properties of recombinant **gelatinase** A C domain to extracellular matrix and basement membrane components
AUTHOR(S): Wallon, U. Margaretha; Overall, Christopher M.
CORPORATE SOURCE: FacultyDentistry, Dep. Biochem. Mol. Biol., Univ. British Columbia, Vancouver, BC, V6T 1Z3, Can.
SOURCE: Journal of Biological Chemistry (1997), 272(11), 7473-7481
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The binding properties of the COOH-terminal hemopexin-like domain (C domain) of human **gelatinase** A (matrix **metalloproteinase** -2, 72-kDa **gelatinase**) were investigated to determine whether the C domain has binding affinity for extracellular matrix and basement membrane components. Recombinant C domain (rC domain) (Gly417-Cys631) was expressed in Escherichia coli, and the purified protein, identified using two antipeptide antibodies, was determined by electrospray mass spectrometry to have a mass of 25,925 Da, within 0.1 Da of that predicted. As assessed by microwell substrate binding assays and by column affinity chromatog., the matrix protein laminin, denatured type I collagen, elastin, SPARC (secreted protein that is acidic and rich in cysteine), tenascin, and Matrigel were not bound by the rC domain. Unlike the hemopexin-like domains of **collagenase** and stromelysin, the rC domain also did not bind native type I collagen. Nor were native or denatured types VII collagen bound. However, binding to heparin and fibronectin (Kd, 1.1+10-6 M) could be disrupted by 0.58-0.76 and 0.3 M NaCl, resp. Using nonoverlapping chymotrypsin-generated fragments of fibronectin, binding sites for the rC domain were found on both the 40-kDa heparin binding and the 120-kDa cell binding fibronectin domains (Kd values, .apprx.4-6+10-7 M). The Ca2+ ion, but not the potential structural Zn2+ ion, were found to be essential for maintaining the binding properties of the protein. The apo-form of the rC domain did not bind

heparin, and both EDTA and the specific Ca2+ ion chelator 1,2-bis(2-aminophenoxy) ethane-N,N,N',N'-tetraacetic acid, but not the Zn2+ ion chelator 1,10-phenanthroline, eluted the holo form of the rC domain from both heparin-Sepharose and fibronectin. Inductive coupled plasma mass spectrometry also did not detect a Zn2+ ion in the rC domain. In contrast, reduction with 65 mM dithiothreitol did not interfere with heparin binding, further emphasizing the crucial structural role played by the Ca2+ ion. Together, these data demonstrate for the first time that the hemopexin-like domain of **gelatinase** A has a binding site for fibronectin and heparin, and that Ca2+ ions are important in maintaining the structure and function of the domain.

IT **9005-49-6**, Heparin, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(hemopexin-like domain (C domain) of human **gelatinase** A (matrix **metalloproteinase**-2) requires Ca2+ for fibronectin and heparin binding)

RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L4 ANSWER 25 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:142675 CAPLUS
DOCUMENT NUMBER: 126:236484
TITLE: Misregulation of stromelysin-1 expression in mouse mammary tumor cells accompanies acquisition of stromelysin-1-dependent invasive properties
AUTHOR(S): Lochter, Andre; Srebrow, Anabella; Sympson, Carolyn J.; Terracio, Nathan; Werb, Zena; Bissell, Mina J.
CORPORATE SOURCE: Life Sciences Division, Lawrence Berkeley National Laboratory, University of California, Berkeley, CA, 94720, USA
SOURCE: Journal of Biological Chemistry (1997), 272(8), 5007-5015
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Stromelysin-1 is a member of the **metalloproteinase** family of extracellular matrix-degrading enzymes that regulates tissue remodeling. We previously established a transgenic mouse model in which rat stromelysin-1 targeted to the mammary gland augmented expression of endogenous stromelysin-1, disrupted functional differentiation, and induced mammary tumors. A cell line generated from an adenocarcinoma in one of these animals and a previously described mammary tumor cell line generated in culture readily invaded both a reconstituted basement membrane and type I collagen gels, whereas a nonmalignant, functionally normal epithelial cell line did not. Invasion of Matrigel by tumor cells was largely abolished by **metalloproteinase** inhibitors, but not by inhibitors of other proteinase families. Inhibition expts. with antisense oligodeoxynucleotides revealed that Matrigel invasion of both cell lines was critically dependent on stromelysin-1 expression. Invasion of collagen, on the other hand, was reduced by only 40-50%. Stromelysin-1 was expressed in both malignant and nonmalignant cells grown on plastic substrata. Its expression was completely inhibited in nonmalignant cells,

but up-regulated in tumor cells, in response to Matrigel. Thus misregulation of stromelysin-1 expression appears to be an important aspect of mammary tumor cell progression to an invasive phenotype.

IT **9005-49-6**, Heparin, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(misregulation of stromelysin-1 expression in mouse mammary tumor cells accompanies acquisition of stromelysin-1-dependent invasive properties in relation to)
RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L4 ANSWER 26 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:141789 CAPLUS
DOCUMENT NUMBER: 126:223430
TITLE: Differential regulation of extracellular matrix **metalloproteinase** and tissue inhibitor by heparin and cholesterol in fibroblast cells
AUTHOR(S): Tyagi, Suresh C.; Kumar, Suresh; Katwa, Laxmansa
CORPORATE SOURCE: Medical Center, University of Mississippi, Jackson, MS, 39216-4505, USA
SOURCE: Journal of Molecular and Cellular Cardiology (1997), 29(1), 391-404
CODEN: JMCDAY; ISSN: 0022-2828
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Heparin has been shown to stimulate angiogenesis in the border zones surrounding infarcted myocardium. Matrix **metalloproteinases** (**MMP**), which are involved in extracellular matrix (ECM) organization, have also been shown to be activated. Cholesterol is required for receptor signaling in the plasma membrane, but a role of **MMPs** for cholesterol in ECM remodeling has not yet been shown. To examine whether heparin and cholesterol induce **MMP** and tissue inhibitor of **metalloproteinase** (TIMP) in human heart fibroblast (HHF) cells, confluent HHF cells were treated with cholesterol (100 μM) or heparin (20 μM). **MMP** activity was measured using zymog. and TIMP was measured by Western blot anal. The number of HHF cells, measured by a hemocytometer, increased after heparin or cholesterol treatment. **Gelatinase** A (**MMP**-2) activity increased in heparin treated cells, and the TIMP-1 level increased in cholesterol-treated cells. Based on Northern blot anal., we observed that both **MMP**-1 and **MMP**-2 were induced at the gene transcription level by heparin and that TIMP-1 was induced by cholesterol. To examine whether the effects of heparin and cholesterol were due to Ca2+ mobilization, we carried out Ca2+ transient assays using FURA-2/AM as a fluorescence probe in HHF cells. Heparin induced a slow rise in the Ca2+ transient with a slow decay, and cholesterol induced a rapid rise with a slow reversal to the baseline calcium level. This suggested that the effect of heparin on Ca2+ release from HHF may be secondary to the receptor binding on the cell membrane but that cholesterol may have a direct effect. Protein kinase inhibitor and Ca2+-channel blocker have been shown to inhibit **MMP** expression. To examine whether the effect of heparin on **MMP** expression is mediated through the **collagenase** promoter activity, we carried out gel-shift assays

using a 21-oligonucleotide analog to the **MMP**-1 promoter sequence. Results suggested that the increase in **MMP** promoter activity by heparin is due to a specific transcription factor binding to **MMP**-1 promoter sequence. The effect of cholesterol on fibroblast cell proliferation is due to the tissue inhibitor. This study demonstrated the role of heparin and cholesterol in ECM remodeling and has implications for angiogenesis and atherosclerosis, resp.

IT **9005-49-6**, Heparin, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(regulation of extracellular matrix **metalloproteinase** and tissue inhibitor by heparin and cholesterol in heart fibroblasts)

RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L4 ANSWER 27 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:337257 CAPLUS
DOCUMENT NUMBER: 125:54278
TITLE: Stimulation of **collagenase** (matrix **metalloproteinase**-1) synthesis in histiotypic epithelial cell culture by heparin is enhanced by keratinocyte growth factor
AUTHOR(S): Putnins, Edward E.; Firth, James D.; Uitto, Veli-Jukka
CORPORATE SOURCE: Dep. of Oral Biology, Univ. of British Columbia, Vancouver, BC, Can.
SOURCE: Matrix Biology (1996), 15(1), 21-29
CODEN: MTBOEC; ISSN: 0945-053X
PUBLISHER: Fischer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The role of heparin and heparan sulfate in the control of epithelial **collagenase** production was investigated utilizing a histiotypic cell culture model. The effect of keratinocyte growth factor (KGF), a heparin-binding growth factor, on **collagenase** secretion was also examined Heparin, and, to a lesser extent, heparan sulfate induced release of a 58-kDa, gelatin-degrading enzyme which was subsequently identified as the **collagenase**, matrix **metalloproteinase**-1. The increase in **collagenase** secretion by heparin was further enhanced by the addition of KGF. KGF alone did not have any effect. Anal. of secreted radiolabeled proteins showed that the increase in **collagenase** activity was not due to a general increase in protein synthesis. Synthesis of **collagenase** protein was specifically increased by heparin and further increased by KGF plus heparin. Heparin and heparan sulfate in combination with KGF may thus have important roles in the regulation of epithelial cell **collagenase** under conditions such as inflammation and wound healing.

IT **9005-49-6**, Heparin, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(stimulation of **collagenase** (matrix **metalloproteinase** -1) synthesis in histiotypic epithelial cell culture by heparin is enhanced by keratinocyte growth factor)

RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L4 ANSWER 28 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:674888 CAPLUS
DOCUMENT NUMBER: 123:189212
TITLE: Keratinocyte growth factor stimulation of **gelatinase** (matrix **metalloproteinase** -9) and plasminogen activator in histiotypic epithelial cell culture
AUTHOR(S): Putnins, Edward E.; Firth, James D.; Uitto, Veli-Jukka
CORPORATE SOURCE: Faculty of Dentistry, University of British Columbia, Vancouver, BC, Can.
SOURCE: Journal of Investigative Dermatology (1995), 104(6), 989-94
CODEN: JIDEAE; ISSN: 0022-202X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The purpose of this investigation was to examine the role that keratinocyte growth factor (KGF) plays in the control of matrix-degrading protease activity in epithelial cells. The culture conditions had a significant effect on cellular responses to the growth factor. In histiotypic culture on porous-polycarbonate membranes, porcine periodontal ligament epithelial cells responded to KGF with increased 92-kDa **gelatinase** (matrix **metalloproteinase** [**MMP**]-9) activity. No such response was observed in cells maintained on plastic plates. Epidermal growth factor and platelet-derived growth factor also increased **MMP**-9 activity in the histiotypic cultures of epithelial cells. Addition of heparin with KGF produced a further increase in **MMP**-9 activity, with heparin alone having no effect. Precoating of polycarbonate membranes with matrix components showed that fibronectin and an engineered poly-RGD mol. substrate were required for KGF plus heparin to increase **MMP**-9 activity. Precoating plastic culture plates with the same proteins did not generate the same response. Concomitant with **gelatinase** activity, KGF also increased urokinase-type plasminogen activator in the epithelial cells. Thus, KGF appears to be an important regulator of protease secretion in epithelial cells.
IT **9005-49-6**, Heparin, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(enhancement of keratinocyte growth factor stimulation of **gelatinase** in epithelial culture)
RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L4 ANSWER 29 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:645998 CAPLUS
DOCUMENT NUMBER: 123:109421
TITLE: Collagen and **collagenase** mRNAs in normal and sclerotic glomeruli: predictors of progression and response to therapy
AUTHOR(S): He, Ci-Jiang; Yang, Chih-Wei; Peten, Emmanuel P.; Liu, Zhi-Hong; Patel, Anita; Striker, Liliane J.; Striker, Gary E.

CORPORATE SOURCE: Renal Cell Biology Section, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, USA
SOURCE: Kidney International, Supplement (1995), 49, S39-S43
CODEN: KISUDF; ISSN: 0098-6577
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Progressive glomerulosclerosis is associated with decreasing kidney function, eventuating in end-stage renal failure. There are multiple components of the extracellular matrix, and the exact composition in various renal diseases is not known. Thus, we examined some of the major components of the extracellular matrix (ECM) in murine and human glomerular diseases. We studied matrix synthesis and degradation at the level of gene expression and ECM composition in the intact glomerulus. To determine whether the composition of sclerosis was similar among diseases, we examined a normal mouse strain and compared it with strains which spontaneously developed glomerulosclerosis. The baseline levels of matrix components varied between different mouse strains, and this level correlated with their propensity to develop glomerulosclerosis. In addition, when glomerulosclerosis was induced, the baseline ECM mRNA level predicted the subsequent outcome. We studied mice transgenic for bovine growth hormone, since they develop progressive glomerulosclerosis. Treatment with heparin substantially decreased the lesions without changes in type IV collagen mRNAs. However, there was an up-regulation of both the mRNA and enzyme activity for the 92 kD matrix **metalloproteinase**. In contrast, when these mice were treated with either angiotensin converting enzyme inhibitors or angiotensin II (Ang II) receptor antagonists, the glomerulosclerosis was accentuated histol. and the ECM synthetic and degradative mRNAs were elevated. These data suggest that the mRNA levels reflect response to therapy. We examined glomeruli from human nephrectomy specimens and found an increase in the mRNA levels for both the synthetic and degradative components of the ECM in those specimens with glomerulosclerosis. Preliminary examination of glomeruli isolated from renal biopsies reveals homogeneity in the α2/α3IV ratio among diabetics, but not among those with IgA nephropathy. These data suggest that modifications in ECM gene regulation may serve as predictors of progression.

IT **9005-49-6**, Heparin, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(collagen and **collagenase** mRNAs in human and laboratory animal normal and sclerotic glomeruli as predictors of progression and response to therapy)

RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L4 ANSWER 30 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:291107 CAPLUS
DOCUMENT NUMBER: 122:77358
TITLE: Heparin and its derivatives modulate serine proteinases (SERPS) serine proteinase inhibitors (SERPINS) balance: Physiopathological relevance
AUTHOR(S): Hornebeck, W.; Lafuma, C.; Robert, L.; Moczar, M.; Moczar, E.

CORPORATE SOURCE: Faculte de Medecine, Universite Paris XII, Creteil, Fr.
SOURCE: Pathology, Research and Practice (1994), 190(9-10), 895-902
CODEN: PARPDS; ISSN: 0344-0338
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 30 refs. Heparin and heparan sulfate, exhibiting wide biol. interactions, are constituted of block structures. A defined pentasaccharide motif was found responsible for the enhancement of the rate of inactivation of factor Xa by antithrombin III. Heparin also interacts with other serine proteinase inhibitors as protease nexin I, and thus possibly modulates extracellular matrix proteolysis by serine proteinases in the pericellular environment. Human neutrophil elastase (HNE) activity is inhibited by heparin with Ki = 75 pM. This strong interaction is electrostatic, involving HNE/arginine residues disposed in a "cluster shoe" arrangement on the surface of the mol. and mainly OSO3-groups of heparin. HNE-heparin interactions also interfere with HNE assocns. with its natural inhibitors: it decreases the rate of association of HNE with α1 proteinase inhibitor (α1Pi) by 3 orders of magnitude, while increasing Kass between HNE and mucus bronchial inhibitor (MBI) by>10 fold. In vivo expts. demonstrated that heparin fragments lacking anticoagulant activity were able to nearly completely abolish emphysematous lesions induced in mice by a single intratracheal administration of 200 μg HNE. Long chain unsatd. fatty acids peptide conjugates were described as competitive HNE inhibitors (Hornebeck W. et al. 1985). We synthesized N-oleoyl heparin derivative (3 oleoyl groups/one mol. of heparin); such a lipophilic glycosaminoglycan (LipoGAG), although acting as an elastin protecting agent, possessed lower HNE inhibitory capacity as compared with heparin. In contrast, however, it was able to inhibit other serine proteinases such as urokinase, plasmin, porcine pancreatic α-chymotrypsin and elastase. Such Lipo GAG's can be therefore useful to control matrix **metalloproteinases** (**MMPs**) during tissue remodeling or tumor invasion.

IT **9005-49-6**, Heparin, biological studies
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(serine proteinases and serine proteinase inhibitors mediation by heparin and its derivs.)

RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L4 ANSWER 31 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:695795 CAPLUS
DOCUMENT NUMBER: 121:295795
TITLE: Reciprocated matrix **metalloproteinase** activation: A process performed by interstitial **collagenase** and progelatinase A
AUTHOR(S): Crabbe, Thomas; O'Connell, James P.; Smith, Bryan J.; Docherty, Andrew J. P.
CORPORATE SOURCE: Department of Oncology, Celltech Research, Slough, SL1 4EN, UK
SOURCE: Biochemistry (1994), 33(48), 14419-25
CODEN: BICHAW; ISSN: 0006-2960

DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Gelatinase** A, a member of the matrix **metalloproteinase** (**MMP**) family, is secreted possessing an 80 amino acid N-terminal propeptide that must be removed to generate the active enzyme. Purified progelatinase A was activated to 38% of maximum by a 6 h incubation at 37° with equimolar concns. of trypsin-activated interstitial **collagenase** (another **MMP**). The increase in activity was accompanied by cleavage of the Mr 72 000 progelatinase A to the Mr 66 000 active enzyme that has Y81 as its N-terminus. At low concns., progelatinase A was processed via an inactive intermediate, suggesting that its activation is a biphasic process. This was confirmed by the action of **collagenase** on proE375→A (a mutant of progelatinase A that cannot become active) because, in this instance, only an Mr 68 000 species with L38 as the N-terminus was produced. The remaining propeptide amino acids to Y81 could be readily removed by added active **gelatinase** A, indicating that **collagenase** works by generating an intermediate that is susceptible to autolytic activation. Although relatively slow, the rate of activation could be increased approx. 10-fold by the addition of 100 μg/mL heparin. This binds to the C-terminal domain of **collagenase** and progelatinase A and presumably acts as a template that positions the reactants close to one another. **Collagenase** activated by trypsin retains 8 or 14 amino acids of its propeptide. The activated **gelatinase** A was able to remove these by cleaving the Q80-F81 peptide bond, an event that has been shown to significantly increase the activity of **collagenase** against fibrillar collagen. The fact that the complete degradation of native collagen requires the activities of both a **collagenase** and a **gelatinase** provides a functional basis for this reciprocated mechanism of activation.
IT **9005-49-6**, Heparin, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(heparin binding in relation to reciprocated activation of matrix **metalloproteinases** interstitial **collagenase** and progelatinase A)
RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L4 ANSWER 32 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:628552 CAPLUS
DOCUMENT NUMBER: 121:228552
TITLE: Angiogenic potential in vivo by Kaposi's sarcoma cell-free supernatants and HIV-1 tat product: inhibition of KS-like lesions by tissue inhibitor of **metalloproteinase**-2
AUTHOR(S): Albini, Adriana; Fontanini, Gabriella; Masiello, Luciana; Tacchetti, Carlo; Bigini, Daniela; Luzzi, Paola; Noonan, Douglas M.; Stetler-Stevenson, William G.
CORPORATE SOURCE: National Institute Research Cancer, Genoa, Italy
SOURCE: AIDS (London, United Kingdom) (1994), 8(9), 1237-44
CODEN: AIDSET; ISSN: 0269-9370
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors studied the neoplastic nature of Kaposi's sarcoma (KS). A highly vascularized lesion, KS is frequently associated with AIDS, indicating HIV products may be involved. The authors determined the angiogenic properties of KS cell-secreted products and the HIV-1-tat gene product in vivo. Cell-free secreted products (KS-CM) from cultured epidemic and sporadic KS spindle cells or recombinant (r) HIV-1 tat protein were injected into mice with a matrix support (Matrigel). KS-CM produced lesions carrying all the phenotypic hallmarks of KS, as observed by light and electron microscopy: spindle-shaped cells, hemorrhages and an inflammatory infiltrate, as well as Factor VIII-pos. endothelial cells lining new blood vessels. Electron microscopy indicated an initial granulocyte invasion, with spindle-cell migration and neocapillary formation in the center of the matrix. These lesions required the cofactor heparin; KS-CM or heparin alone were poorly angiogenic. A less intense angiogenesis, with lower cellularity and few granulocytes, was observed in basic fibroblast growth factor (bFGF)/heparin lesions, indicating that factors other than bFGF are present in the KS spindle-cell products. When the **collagenase** inhibitor tissue inhibitor of **metalloproteinases** (TIMP)-2 was added to the sponges, KS-CM-induced angiogenesis was reduced by approx. 65% and bFGF-induced angiogenesis inhibited completely. Recombinant HIV-1 tat protein, a growth factor for KS cells, induced vascularization that was also enhanced by heparin, implying that HIV-1 tat could contribute to the etiol. of HIV-associated KS. KS-like lesions were obtained by injecting cell-free secreted products, suggesting that KS is a self-propagating proliferative lesion caused by a cytokine imbalance and not a true neoplasm. Heparin-binding factors appear to be involved and HIV-1 tat angiogenic properties implicate this mol. in AIDS-associated KS. Inhibition of KS-CM-induced KS-like lesions by TIMP-2 suggests that **metalloproteinase** inhibitors could be potential therapeutic agents for KS.

IT **9005-49-6**, Heparin, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(HIV-1 tat protein and tissue inhibitor of **metalloproteinase** -2 effect on angiogenic potential of Kaposi's sarcoma in relation to)

RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L4 ANSWER 33 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:477015 CAPLUS
DOCUMENT NUMBER: 121:77015
TITLE: Activation of human interstitial procollagenase through direct cleavage of the Leu83-Thr84 bond by mast cell chymase
AUTHOR(S): Saarinen, Juhani; Kalkkinen, Nisse; Welgus, Howard G.; Kovanen, Petri T.
CORPORATE SOURCE: Wihuri Res. Inst., Helsinki, SF-00140, Finland
SOURCE: Journal of Biological Chemistry (1994), 269(27), 18134-40
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In inflamed tissue sites characterized by on-going matrix degradation, the matrix **metalloproteinases** are secreted as latent precursors which are capable of proteolysis only after extracellular activation.

Such areas often contain locally increased nos. of mast cells capable of releasing complexes between heparin proteoglycans and fully active endopeptidases with either tryptic (tryptase) or both tryptic and chymotryptic (chymase) activity. The authors have examined the ability of purified human skin chymase to activate human interstitial procollagenase (matrix **metalloproteinase**-1) in the absence and presence of heparin, the physiol. associate of chymase. Chymase activates procollagenase in a time- and concentration-dependent manner. Heparin was found to increase markedly the rate at which chymase activates procollagenase both by accelerating the cleavage of procollagenase and also by preventing its further degradation Chymase activates procollagenase directly by cleaving the Leu83-Thr84 bond, without formation of any intermediate species. This is a novel mechanism for procollagenase activation, which contrasts sharply with the activation mechanisms of other activators studied os far. The ability of chymase to activate procollagenase suggests that chymase plays an active role in matrix degradation at tissue sites where mast cells coexist with extracellular procollagenase.

IT **9005-49-6**, Heparin, miscellaneous
RL: MSC (Miscellaneous)
(human interstitial procollagenase activation by mast cell chymase enhanced by)
RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L4 ANSWER 34 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:400501 CAPLUS
DOCUMENT NUMBER: 121:501
TITLE: Heparin inhibits the induction of three matrix **metalloproteinases** (stromelysin, 92-kD **gelatinase**, and **collagenase**) in primate arterial smooth muscle cells
AUTHOR(S): Kenagy, Richard D.; Nikkari, Seppo T.; Welgus, Howard G.; Clowes, Alexander W.
CORPORATE SOURCE: Dep. Surg., Univ. Washington, Seattle, WA, 98195, USA
SOURCE: Journal of Clinical Investigation (1994), 93(5), 1987-93
CODEN: JCINAO; ISSN: 0021-9738
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Heparin inhibits the migration and proliferation of arterial smooth muscle cells and modifies the extracellular matrix. These effects may be the result of heparin's effects on proteinases that degrade the matrix. The authors have previously reported that heparin inhibits the induction of tissue-type plasminogen activator and interstitial **collagenase** mRNA. The authors have investigated the possibility that heparin affects other members of the matrix **metalloproteinase** family. Phorbol ester increased the levels of mRNA of **collagenase**, 92-kD **gelatinase** and stromelysin as well as the synthesis of these proteins. These effects were inhibited by heparin, but not by other glycosaminoglycans, in a dose-dependent manner. The induction of these matrix **metalloproteinases** was also inhibited by staurosporine and pretreatment with phorbol ester indicating the involvement of the protein kinase C pathway. In contrast, the 72-kD **gelatinase** was expressed constitutively and was not affected by phorbol ester or heparin. Tissue inhibitor of **metalloproteinases**-1 was expressed

constitutively and was slightly increased by phorbol ester. It was not affected by heparin. Thus, heparin inhibits the production of four proteinases (tissue plasminogen activator, **collagenase**, stromelysin and 92-kD **gelatinase**) that form an interdependent system capable of degrading all the major components of the extracellular matrix.

IT **9005-49-6**, Heparin, biological studies
RL: BIOL (Biological study)
(**metalloproteinases** formation inhibition by, in arterial muscle cells, extracellular matrix degradation and cell migration in relation to)
RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L4 ANSWER 35 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:95710 CAPLUS
DOCUMENT NUMBER: 120:95710
TITLE: Effect of tetracyclines which have **metalloproteinase** inhibitory capacity on basal and heparin-stimulated bone resorption by chick osteoclasts
AUTHOR(S): Chowdhury, M. H.; Moak, S. A.; Rifkin, B. R.; Greenwald, R. A.
CORPORATE SOURCE: Div. Rheumatol., Long Island Jew. Med. Cent., New Hyde Park, NY, 11042, USA
SOURCE: Agents and Actions (1993), 40(1-2), 124-8
CODEN: AGACBH; ISSN: 0065-4299
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Several tetracyclines (TETs) are potent inhibitors of **collagenase** (CGase) and can inhibit connective tissue degradation in a variety of inflammatory and degenerative disorders. The role of CGase in bone resorption by osteoclasts (OC) remains unclear. Disaggregated OCs from chick embryos were cultured for 24 h on devitalized bovine cortical bone ± heparin in the presence of various TETs. Doxycycline (Dox) inhibited pit formation in a dose-dependent manner. CMT, a TET derivative which inhibits matrix **metalloproteinases** (**MMPs**) but is not antimicrobial, also inhibited chick OC bond resorption. Heparin markedly stimulated bone resorption at 5 μg/mL, which was reversed by Dox, 5 μg/mL. TETs can reversibly inhibit both basal and heparin-stimulated bone resorption by chick OCs. These findings suggest that **MMPs** may play a role in osteoclastic bone resorption, and that safe and effective inhibitors of **MMPs**, including certain TETs, might have a potential therapeutic role.

IT **9005-49-6**, Heparin, biological studies
RL: BIOL (Biological study)
(bone resorption by osteoclasts stimulation by, tetracyclines inhibition of)
RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L4 ANSWER 36 OF 36 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1993:93693 CAPLUS

DOCUMENT NUMBER: 118:93693
TITLE: A simple, quantitative method for assessing angiogenesis and antiangiogenic agents using reconstituted basement membrane, heparin, and fibroblast growth factor
AUTHOR(S): Passaniti, Antonino; Taylor, Robert M.; Pili, Roberto; Guo, Yue; Long, Peter V.; Haney, Joseph A.; Pauly, Rebecca R.; Grant, Derrick S.; Martin, George R.
CORPORATE SOURCE: Gerontol. Res. Cent., Natl. Inst. Aging, Bethesda, MD, USA
SOURCE: Journal of Neurosurgery (1992), 77(5), 519-28
CODEN: JONSAC; ISSN: 0022-3085
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Blood vessel growth is necessary for normal tissue homeostasis and contributes to solid tumor growth. Methods to quantitate neovascularization should be useful in testing biol. factors and drugs that regulate angiogenesis or to induce a vascular supply a promote wound healing. An extract of basement membrane proteins (matrigel) was found to reconstitute into a gel when injected s.c. into C57/BL mice and to support an intense vascular response when supplemented with angiogenic factors. New vessels and von Willebrand factor antigen staining were apparent in the gel 2-3 days after injection, reaching a maximum after 3-5 days. Hb content of the gels was found to parallel the increase in vessels in the gel allowing ready quantitation. Angiogenesis was obtained with both acidic and basic fibroblast growth factors and was enhanced by heparin. Several substances were tested for angiostatic activity in this assay by coinjection in Matrigel with fibroblast growth factor and heparin. Platelet-derived growth factor BB, interleukin 1-β, interleukin 6, and transforming growth factor-β were potent inhibitors of neovascularization induced by fibroblast growth factor. Tumor necrosis factor-α did not alter the response but was alone a potent inducer of neovascularization when coinjected with Matrigel and heparin. Consistent with the previously demonstrated importance of **collagenase** in mediating endothelial cell invasion, a tissue inhibitor of **metalloproteinases** that also inhibits **collagenases** was found to be a potent inhibitor of fibroblast growth-induced angiogenesis. Our assay allows the ready quant. assessment of angiogenic and antiangiogenic factors and should be useful in the isolation of endothelial cells from the capillaries that penetrate into the gel.
IT **9005-49-6**, Heparin, biological studies
RL: BIOL (Biological study)
(angiogenesis affecting agents bioassay in mouse using matrigel and fibroblast growth factor and)
RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

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     (FILE 'HOME' ENTERED AT 10:32:14 ON 20 MAR 2003)

     FILE 'REGISTRY' ENTERED AT 10:32:27 ON 20 MAR 2003
               E "ENOXAPARIN"/CN 25
L1             2 S E3 OR E4

     FILE 'CAPLUS' ENTERED AT 10:32:48 ON 20 MAR 2003
L2         21300 S L1
L3            60 L2 AND METALLOPROTEINASE?
L4            36 L3 AND (COLLAGENASE? OR AGGRECANASE? OR GELATINASE? OR MMP)

     FILE 'STNGUIDE' ENTERED AT 10:34:22 ON 20 MAR 2003

     FILE 'CAPLUS' ENTERED AT 11:01:16 ON 20 MAR 2003
L5            37 L3 AND (COLLAGENASE? OR AGGRECANASE? OR GELATINASE? OR MMP OR A
L6             1 L5 NOT L4

=> d l6 ibib abs hitstr

L6   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2002:541384  CAPLUS
DOCUMENT NUMBER:          138:22953
TITLE:                    Von Willebrand factor-cleaving protease (ADAMTS13) in
                          thrombocytopenic disorders: a severely deficient
                          activity is specific for thrombotic thrombocytopenic
                          purpura
AUTHOR(S):                Bianchi, Valentina; Robles, Rodolfo; Alberio, Lorenzo;
                          Furlan, Miha; Lammle, Bernhard
CORPORATE SOURCE:         Central Hematology Laboratory, University Hospital,
                          Inselspital, Bern, CH-3010, Switz.
SOURCE:                   Blood (2002), 100(2), 710-713
                          CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER:                American Society of Hematology
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   A severe deficiency in von Willebrand factor-cleaving protease (ADAMTS13)
     activity (< 5% that in normal plasma) has been observed in most patients with
     a diagnosis of thrombotic thrombocytopenic purpura (TTP) but not in those
     with a diagnosis of hemolytic uremic syndrome.  However, ADAMTS13
     deficiency has been claimed not to be specific for TTP, since it was observed
     in various thrombocytopenic and other conditions.  We studied 68 patients
     with thrombocytopenia due to severe sepsis or septic shock (n = 17),
     heparin-induced thrombocytopenia (n = 16), idiopathic thrombocytopenic
     purpura (n = 10), or other hematol. (n = 15) or miscellaneous conditions (n =
10).
     Twelve of the 68 patients had subnormal levels of ADAMTS13 activity
     (≤ 30%), but none had less than 10%.  Thus, the study showed that
     ADAMTS13 activity is decreased in a substantial proportion of patients
     with thrombocytopenia of various causes.  A severe deficiency of ADAMTS13
     (< 5%), identified in more than 120 patients during 1996 to 2001 in our
     laboratory, is specific for a thrombotic microangiopathy commonly labeled TTP.
IT   9005-49-6, Heparin, biological studies
     RL: ADV (Adverse effect, including toxicity); BSU (Biological study,
     unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (induced-thrombocytopenia; metalloproteinase ADAMTS13 in
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human with thrombocytopenic disorders and thrombotic thrombocytopenic purpura)
RN 9005-49-6 CAPLUS
CN Heparin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT